ABSTRACT

Methods for reducing or inhibiting the irreversible inactivation of water-soluble biologically active agents in biodegradable polymeric delivery systems which are designed to release such agents over a prolonged period of time, such as PLGA delivery systems are provided.. The method comprises preparing a PLGA delivery systems whose microclimate, i.e. the pores where the active agent resides, uniformly or homogenously maintain a pH of between 3 and 9, preferably between 4 and 8, more preferably between 5 and 7.5 during biodegradation. Depending on the size of the delivery system, and the initial bulk permeability of the polymer, this result is achieved by (a) incorporating a water-soluble carrier into the delivery system, (b) incorporating a select basic additive (or antacid) into the delivery system, (c) incorporating both a water soluble carrier and a select basic additive into the delivery system, (d) adding a pore forming molecule for increasing the rate of release of low molecular weight monomers and oligomers into the delivery system, (e) using a PLGA polymer with reduced glycolide content, i.e. PLGA with from 100% to 75% lactide and 0 to 25% glycolide) (f) using a microencapsulation method that yields a more extensive pore-network, e.g. oil-in-oil emulsion-solvent extraction as opposed to water-in-oil-in water-solvent evaporation method, and (g) combinations thereof.